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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Thomas L. Benjamin et al.	Art Unit:	1632
Serial No.:	09/812,633	Examiner:	Q. Janice Li
Filed:	March 19, 2001	Customer No.:	21559
Title:	DIAGNOSING AND TREATING CANCER CELLS USING SAL2		

Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. § 1.132 OF DR. THOMAS BENJAMIN, PhD

I declare:

1. I am an inventor of the subject matter that is described and claimed in the above-captioned patent application.

2. I have read the Office Action mailed on August 14, 2002 in connection with the above-referenced patent application.

3. We have found multiple polymorphisms in the Sal2 gene using techniques known in the art at the time the application was filed. For example, we have described

in the specification a polymorphism (on pages 36 and 37) at amino acid position 73 of the $p150^{Sal2}$ protein, characterized by the substitution of a serine residue with a proline residue. Referring to Figure 11, we have found loss of heterozygosity (LOH) at this site, or loss of the 73S allele, in an ovarian tumor relative to healthy tissue. Page 36 (line 28) of the specification also discloses of a G744R substitution in ovarian carcinoma cell lines, which we have also found in human ovarian tumor samples. In addition to the S73C and the G744R polymorphisms in the $p150^{Sal2}$ gene described throughout the specification (e.g., at pages 36 and 37), multiple polymorphisms associated with proliferative diseases have been found elsewhere in the $p150^{Sal2}$ gene (summarized in Exhibit 1). Tumor samples and matching healthy tissues isolated from heterozygous individuals were analyzed for LOH at such polymorphic positions. In particular, LOH at amino acid position 120 (S120P) was only observed in tumor samples (P/P) while healthy tissues were heterozygous (S/P). Based on our analysis of ovary tumor and normal tissue screened to date, we have found that LOH only occurs in tumor samples.

4. Exhibit 2 demonstrates that we have also found $p150^{Sal2}$ to be down regulated in a number of human tumors, in addition to ovarian cancer. Ubiquitin normalized cDNA arrays (Clontech), containing matched normal and tumor tissues from cancer patients, were hybridized with a p150 cDNA (*Sal2*) to analyze $p150^{Sal2}$ protein expression. Such arrays included the cDNA from 14 samples of kidney tumors and 11

samples of colon tumors. Out of fourteen kidney tumor samples, ten had a marked down regulation of $p150^{Sal2}$ gene product relative to normal control tissues (about 70% of tumors). Similarly, out of eleven of the colon tumor samples tested, eleven showed a down regulation of $p150^{Sal2}$ (100%). Based on this analysis, a down regulation of the protein is clearly associated with colon and kidney cancers. Techniques to detect protein levels were known in the art at the time of filing of the application and are provided, for example, in the specification on page 20 (lines 11-24).

5. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

2/14/03
Date

Dr. Thomas Benjamin

EXHIBIT 1

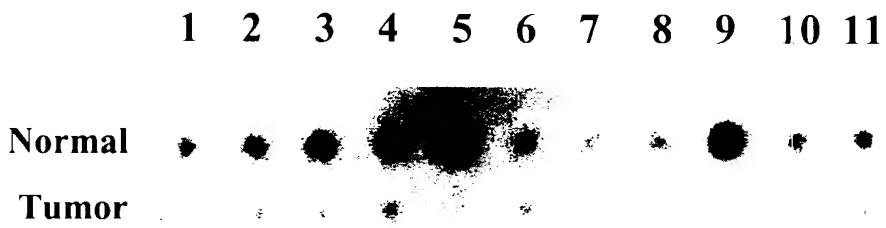
Summary of mutations or polymorphism found in $p150^{sal2}$ gene in ovarian tumors.

AA number	Dominant allele	Mutated or polymorphoic allele
73	Serine (S)	Cysteine (C) * heterozygous S/C Found in both tumor and normal tissues normal tissue
120	Serine (S)	Proline (P) ** heterozygous S P and homozygous P P found only in tumor tissues
166	Proline (P)	Leucine (L) * heterozygous P/L Found in both tumor and normal tissues normal tissue
280	Glycine (G)	Alanine (A) * heterozygous G/A Found in both tumor and normal tissues normal tissue
515	Valine (V)	Glycine (G) * heterozygous V/G Found in both tumor and normal tissues normal tissue
744	Glycine (G)	Arginine (R) * heterozygous G/R Found in both tumor and normal tissues normal tissue
951	Alanine (A)	Glycine (G) * heterozygous A/G Found in both tumor and normal tissues normal tissue

EXHIBIT 2

Kidney Tumors

Colon Tumors



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Guest Experts

David Fishman, M.D., is the Director of the Natic Cancer Early Detection Program (NOCEDP) at North University, as well as an Associate Professor. The NC located in Prentice Women's Hospital and Maternity C Superior Street, Suite 214, Chicago, IL 60611. For ad information, call (312) 926-8400. Dr. Fishman is a boa gynecologic oncologist and has written numerous pee articles.

National Ovarian Cancer Early Detection F at Northwestern

The American Cancer Society estimates that approximately 24,000 diagnosed with ovarian cancer each year. Ovarian cancer is the 5th cause of cancer death among U.S. women and has the highest mor all gynecologic cancers. The majority of women with ovarian cancer diagnosed after the disease has reached an advanced stage (stage because the symptoms of ovarian cancer are vague or "silent". Des aggressive surgical intervention and new chemotherapeutic regimer 5-year survival rate for women with advanced stage ovarian cancer remained constant, over the past 30 years, at approximately 15%. those women diagnosed with cancer confined to the ovary (stage I) overall 5-year survival approaching 90%. Clearly, the need for early ovarian cancer is the best way to improve survival. The National O Early Detection Program aims to do this.

The National Ovarian Cancer Early Detection Program, under the d David A. Fishman, is a collaborative effort between the National Ca Northwestern University and the Robert H. Lurie Comprehensive Ca of Northwestern. This collaborative effort integrates the biochemica ovarian metastasis with the development of new serum and plasma markers for the early detection of ovarian cancer.

The purpose of the National Ovarian Cancer Early Detection Progra (NOCEDP) is to identify those women who are at increased risk for ovarian cancer and to develop new tests, unique to the ovaries, to h ovarian cancer at an early, treatable stage. The requirements to enr

program include one or more of the following: a personal history of l
or urinary cancer; one or more first degree relatives (mother, sister,
with ovarian cancer; multiple family members with either breast and
cancer; a personal history of a positive BRCA1 or BRCA2 genetic te
close relative with a positive BRCA1or BRCA2 genetic test result; a
fertility drugs for more than one year.

Click here for related information.

Created: *11/30/2000 - David Fishman, M.D.*

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